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Leiomyosarcoma of the Urinary Bladder in Adult Patients: A Systematic Review of the Literature and Meta-Analysis

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Keywords
Urological neoplasms · Bladder · Sarcoma · Leiomyosarcoma · Systematic review of the literature · Meta-analysis · Treatment · Mortality

Abstract
Purpose: Leiomyosarcoma of the urinary bladder is exceedingly rare. Most clinicians come across only a few cases during their career, and information regarding treatment and outcome is scattered in the scientific literature. Interested clinicians and patients have to undertake troublesome search for treatment and outcome information. ***Material and methods:*** We performed a systematic review of the literature using the PubMed and Web of Science databases and included all identified cases published in English language between 1970 and June 2018 into a meta-analysis. Prior to the literature search, key questions were formulated and with the data obtained, answers to these questions should be derived. ***Results:*** We analyzed clinical data of 210 cases of urinary bladder leiomyosarcoma revealed by this review and seen in our institution. The mean age of patients was 52 years. The majority (75%) of the tumors was classified as high-grade sarcomas. We found no report of a prior radiation therapy to the pelvic organs, but some authors suggested an association between cyclophosphamide treatment and the development of bladder leiomyosarcoma, especially in patients with retinoblastoma. For the whole sample, we determined 5- and 10-year cancer-specific cumulative mortality rates of 38 and 50%. Patients with high-grade sarcomas had a trend toward a higher mortality compared with low-grade tumors ($p = 0.0280$). The most promising treatment option seems to be surgery (radical or partial cystectomy) with negative resection margins, possibly supplemented by chemotherapy or radiation. ***Conclusion:*** About half of patients with bladder leiomyosarcoma survived on the long run. Low-grade tumors may have a better outcome with, nevertheless, countable long-term mortality. For better assessment of that rare bladder tumor, its best treatment options, and the influence of neoadjuvant or adjuvant therapies on the outcome of patients, a larger series with long-term survival data is required.

Introduction

Non-urothelial neoplasms rarely occur in the urinary bladder. Leiomyosarcoma represents the most common subtype of malignant mesenchymal tumors in this organ but still accounts for less than 1% of all primary bladder tumors [1]. Until now, knowledge about this rare disease

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comes mainly from individual case reports or smaller case series and there is only little information about long-term survival rates. The largest series published was a Surveillance, Epidemiology, and End Results database study enrolling 183 patients treated between 1973 and 2010 [1]. In our study, we performed a systematic review of the literature with meta-analysis of reported cases with sufficient data in order to give clinicians and patients a rapid overview on the knowledge about this rare disease.

Material and Methods

The PubMed and Web of Science databases were used to perform a systematic literature review, based on the criteria described by Galfano and Novara [2]. With the key words "leiomyosarcoma" and "bladder," 386 articles could be retrieved on the PubMed and 232 items on the Web of Science database on June 8, 2018. We only considered articles in English language that were published between 1970 and June 2018. Patients with a primary urinary bladder leiomyosarcoma and a minimum age of 16 years were included. We identified 209 published cases and added 1 unpublished case seen in our institution. Detailed characteristics about all these cases are summarized in an online supplementary Table (see www.karger.com/doi/10.1159/000494357) [3–81]. In some larger series, it was not possible to assign clinical information to each patient [1, 57, 60, 82]. However, when survival details were given for individual cases [57, 60], they were included into the statistical analysis.

The follow-up information of 2 patients seen in our clinic and published earlier [39] was updated. The following key questions were formulated prior to literature search in order to be answered with the data obtained by this review: (1) predisposing factors for the development of bladder leiomyosarcomas; (2) mean age of patients at the time of diagnosis; (3) proportion of primary surgical treatment; (4) sites and time of tumor recurrence; (5) 5- and 10-year cumulative mortality rates of high-grade versus low-grade tumors. The statistical analysis was performed with the Statistical Analysis Systems (SAS Institute Inc., Cary, NC, USA), using competing risk analyses to determine cumulative disease-specific mortality rates and Pepe-Mori tests to compare the mortality curves. All stated percentages are based on the number of articles with existent information about the specific topics, articles with unknown information were not considered.

Results

Overall, 210 cases with data suitable for statistical analysis were identified. Fifty-eight percent of the tumors occurred in males. Age at diagnosis ranged from 16 to 88 years, with a mean age of 52 years. Data on symptoms were available in 91 out of 210 cases (43%). Painless hematuria was the most frequently reported symptom (80%), less common symptoms included dysuria, nocturia, obstructive symptoms, increased frequency of micturition, pelvic and abdominal pain, urinary retention, or recurrent urinary tract infections. The sarcomas had a mean size of 6 cm (range 0.5–16 cm) and 75% were classified as high-grade tumors. None of the patients had a history of radiation therapy of the pelvic organs, but there were 7 cases with radiation of the head and neck region for Hodgkin's or non-Hodgkin's lymphomas and retinoblastomas. Fourteen patients were affected by retinoblastoma in childhood; 9 of them had received a chemotherapy including cyclophosphamide. Altogether, 5 patients had a cyclophosphamide therapy for other diseases. Further, the occurrence of bladder leiomyosarcomas was described for 1 patient with schistosomiasis, 1 with a long-term tamoxifen therapy and 1 with chronic ketamine abuse. Metastases were mentioned only in 4 cases (2%) at the time of diagnosis, twice in the lymph nodes and twice with unknown site.

Seventy-eight percent (n = 120) of the patients with information about therapy (n = 153) underwent primarily surgical treatment (radical cystectomy in 66/153 [43%], partial cystectomy in 54 cases [35%]). Out of these 120 patients, 31 (26%) received a neoadjuvant or adjuvant radiation or chemotherapy in addition to surgery. A total of 26 patients had a transurethral resection of the bladder tumor only with no further reported surgical procedure. Chemotherapy or radiation was the only treatment for 9 patients. In 55 cases, complete resection with negative surgical margin status was reported. Tumor recurrence was observed in 53 out of 210 patients (25%), predominantly locally in the pelvis (18/53 recurrences, 34%) and within the first 3 years after therapy. Distant metastases were mainly located in the lung, liver, or bones. Only 2 late recurrences were reported (8 and 12 years after diagnosis, respectively [31, 53]). The longest documented follow-ups of bladder leiomyosarcoma patients were 20 years after a radical cystectomy [22] and narrowly 22 years after a partial cystectomy ([39], updated follow-up). Disease-specific cumulative mortality rate was 18% after 1 year, 38% after 5 years, and 50% after 10 years for all leiomyosarcoma patients (Fig. 1; Table 1). Compared with patients with high-grade tumors (n = 95), those with low-grade tumors (n = 32) had a lower mortality rate (Fig. 2; Table 1). Disease-specific cumulative mortality rates were 58 and 69% after 5 and 10 years for high-grade sarcomas, 7 and 27% for low-grade sarcomas.

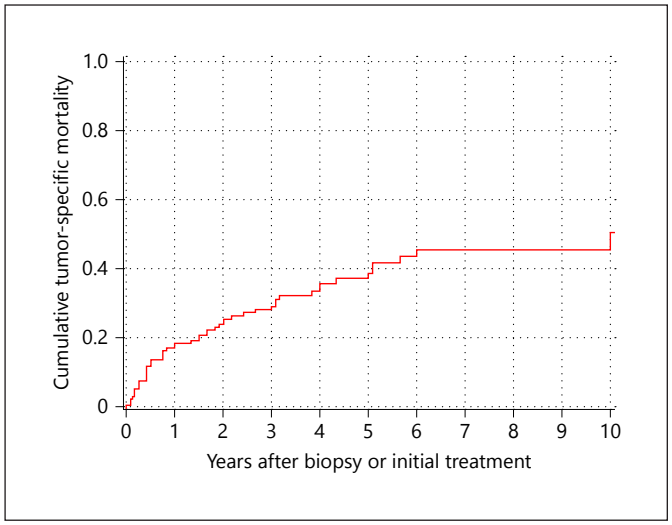

Fig. 1. Cumulative disease-specific mortality rate in the whole sample of tumors with follow-up data allowing meta-analysis (n = 210).

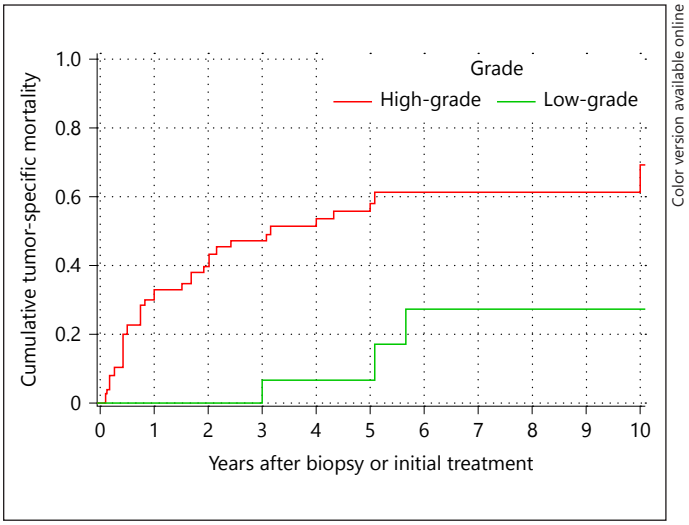

Fig. 2. Cumulative disease-specific mortality rate of high-grade (n = 95) vs. low-grade tumors (n = 32), p = 0.0280. Grading was not available in 83 cases.

Table 1. Disease-specific cumulative mortality rates for the whole sample and separately for low-grade versus high-grade leiomyosarcoma patients after 1, 5 and 10 years with 95% CI and numbers of patients at risk at these time points. Data obtained by systematic review of the literature

Time	Patients at risk, *n*	Cumulative disease-specific mortality rate, %	95% CI
All patients			
1 year	109	18	12–24
5 years	35	38	29–48
10 years	7	50	37–64
Low-grade			
1 year	20	0	Not available
5 years	9	7	0–20
10 years	2	27	6–57
High-grade			
1 year	40	33	22–44
5 years	12	58	44–72
10 years	2	69	50–89

Discussion

With this systematic literature review of all reported cases of urinary bladder leiomyosarcomas since 1970, we were able to analyze the clinical features and survival data of 209 published case reports and 1 added unpublished case seen at our department. It has to be considered that the extent of information varied among the articles and completeness of data could not be achieved. Only the 127 cases with information about tumor grading could be used for the statistical comparison of high-grade and low-grade sarcomas (Fig. 2). Repeatedly, an association between cyclophosphamide treatment and the development of bladder leiomyosarcoma was observed (14 cases). It has been hypothesized that such treatment especially in patients with a genetic retinoblastoma could be a risk factor for this rare bladder tumor [83]. We did not find a case with a prior radiation to the pelvic organs, but to the head and neck region for lymphomas and retinoblastomas suggesting that local radiotherapy plays no major role in the pathogenesis of bladder leiomyosarcoma. A schistosomiasis of the urinary bladder as a documented risk factor for the development of bladder tumors was observed in 1 patient [20, 84]. The reviewed sarcomas were diagnosed at a median age of 52 years, with a male to female ratio of 1.4:1. The frequently used primary treatment was surgery, with radical cystectomy being the most common procedure, followed by partial cystectomy, which can be adequate for smaller tumors. Spiess et al. [85] reported a series of 19 bladder sarcoma patients (mainly leiomyosarcomas) and showed an association between the surgical margin status and the recurrence-free, disease-specific and overall survival. They revealed a 5-year disease-specific survival rate of 59%, which is very close to our results [85]. In our study, we determined 5- and 10-year disease-specific cumulative mortality rates of 38 and 50% for all reviewed bladder leiomyosarcoma patients, 58 and 69%

for patients with a high-grade sarcoma, and 7 and 27% for low-grade tumors. Rosser et al. [82] documented a 5-year disease-specific survival rate of 62% in a series of 36 high-grade bladder leiomyosarcomas that were mainly treated with radical cystectomy, frequently combined with neoadjuvant or adjuvant chemotherapy. Doxorubicin and ifosfamide were the most commonly used regimens. The authors described downstaging in all 4 patients with metastatic disease that received neoadjuvant chemotherapy [82]. We did not identify a case of complete response achieved by chemotherapy alone, but in 1 case treated by radiation following chemotherapy for a low-grade leiomyosarcoma [68], suggesting that multimodal treatment could be beneficial in individual cases of advanced disease. Rodríguez et al. [1] published the largest series of bladder leiomyosarcoma patients so far. They reported 5- and 10-year cancer-specific survival rates of 47 and 35% for 183 patients detected with the Surveillance, Epidemiology and End Results database. Moreover, they showed that an undifferentiated tumor grade, distant disease, and the absence of surgical treatment were associated with a worse outcome [1]. In comparison to our study, they revealed lower cancer-specific survival rates, which may be caused by a higher median age of patients (65 vs. 52 years) or the higher proportion of distant disease at the time of diagnosis (10 vs. 2%). A total of 25% of the patients in our meta-analysis experienced a tumor relapse, which mainly occurred in the pelvis as a local recurrence and within the first 3 years after primary treatment. The lung, liver and bones were common sites for distant metastases. Diagnostic workup should focus on these sites.

This study has several limitations. The information that was obtained from the analyzed case series and single case reports was partially incomplete and the follow-up was limited. It may not be ruled out that there was some publication bias with a preferred reporting of unusual cases and/or cases with apparently successful treatment. Because of the long time period considered with the literature search, it is conceivable that current classification standards would change the histopathological classification of some tumors.

Conclusion

Leiomyosarcoma of the urinary bladder commonly presents as a high-grade tumor. We determined 5- and 10-year cancer-specific cumulative mortality rates of 38 and 50% in this systematic review and meta-analysis of 210 cases. The most important treatment option seems to be surgical resection (radical or partial cystectomy) with negative margins. Surgery can be supplemented by chemotherapy or radiation, especially for metastatic disease or to achieve resectability.

Disclosure statement

The authors declare no conflicts of interest.

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